PP-4
TR-344

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 000344

DATE: October 2, 1979

SUBJECT: Rational for approval of Tebuthiuron Tolerances. CASWELL# 366AA

FROM: Henry Spencer, Ph.D
Toxicology Branch (TS-769)

TO: R. Taylor
Product Manager#

THRU: Dr. Adrian Gross, Chief
Toxicology Branch (TS-769)

Comment:

Dr. Quaife, in a memo dated 9/18/79, was unable to directly calculate an ADI for tebuthiuron. However, a 2 year rat feeding study exhibited a no-effect level of 20 mg/kg which was the level in a 3-generation feeding study producing a reduction in weight gain for the pups.

Dr. Quaife calculated that the exposure from the proposed tolerances would carry an approximate 5400 fold safety factor.

The calulation for a temporary tolerance using a 2000 X safety factor and the 12.5 mg/kg NEL of a 90 day dog study would represent approximately a 3300 X safety factor.

Toxicology Branch considers that additional pertinent information from a 6-month dog study would not be derived with respect to a N.O.E.L. for this chemical to a significantly greater degree than has already been found in that species.

Because the weight gain suppression is considered to be a "minor" effect by several toxicologists in the branch. We concur with Dr. Quaife that the tolerance should be allowed. However, we feel that a NOEL for weight gain can be found by using a 2-generation study as in the proposed Guidelines.

Furthermore, the granting of the tolerance should be contingent upon receipt of written indication to commence within a period of (4) four months, a 2-generation rat reproduction study to be submitted within eighteen (18) months.

Toxicology Branch also proposes that the tolerance be allowed with the registrant fully cognizant of the fact that should adverse data be uncovered the tolerances will become void and recalculated with the appropriate data.

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Redo AS +
2-generation
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EPA FORM 1320-6 (REV. 3-76)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

000341

9/24 10/2/79

DATE: September 18, 1979

SUBJECT: Tebuthiuron, PP No. 7F1925, Elanco submission of 8/1979, TB comment on. (Accession No. 098190)

FROM: TB/HED, M. L. Quaife, Ph.D. MLQ 9/24/79

TO: Mr. R. Taylor, PM

THROUGH: Dr. M. Adrian Gross, Chief
Toxicology Branch/HED
(TS-769)

PP No. 7F1925
EPA File Symbol 147-109-AA

Elanco Products
Indianapolis, Indiana
46206

INTRODUCTION:

Petitioner has sent in (with letter of 8/16/79) a discussion of benefits of use of the formulation of tebuthiuron, Grasland 20P, and of other points in support of requested tolerances for tebuthiuron and its dimethylethyl thiadiazole-containing metabolites at 20 ppm in or on rangeland grass forage and at 2 ppm in or on meat, fat, and meat byproducts of horses, sheep, goats, and cattle. Parts III, IV, and VII relate to hazard evaluation of these tolerances.

Below (on pp. 2 and 3 of this memo, a "free standing summary" of TOX data pertaining to requested tolerances is given; gaps in TOX data needed to support permanent tolerances are noted; and a "margin of safety" for human dietary exposure to tebuthiuron, if requested tolerances are granted, is calculated. In addition, the nature of toxicity of tebuthiuron is discussed, and comments on Petitioner's new submission are made. Finally, two mutagenicity studies on tebuthiuron, not previously covered by TB, are reviewed. (A companion review covers previously unreviewed acute TOX studies on Grasland 20 P.) Discussion/conclusion, pp. 3-4.

RECOMMENDATION:

TB/HED recommends that tolerances requested for tebuthiuron (first paragraph, above) be granted, contingent on Elanco stating in writing, within 30 days, that a new three-generation rat reproduction study on tebuthiuron, which includes lower levels than those previously tested, is underway.

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Tebuthiuron, "free standing summary."

1. Data on technical tebuthiuron considered with regard to tolerance requests.

Oral LD_{50} (rat) = 644 ± 27 (standard error of mean) mg/kg body weight (BW).

Rat, 90-day feeding NOEL = 1,000 ppm.
MEL = 2,500 ppm, with pronounced growth suppression; microscopic pancreatic lesions; and enhanced relative organ weights and liver metabolism (shown in vitro).

Dog, 90-day feeding NOEL = 12.5 mgkg BW/day.
MEL = 25 mg/kg BW/day, effects including increased relative thyroid and spleen weights.

Rat, 2-yr feeding NOEL = 400 ppm (20 mg/kg BW/day).
MEL = 800 ppm (40 mg/kg BW/day), effect being borderline, dose-related growth suppression.

Mouse, 2-yr oncogenicity study: Negative at 1,600 ppm, highest test level, for oncogenicity

Rat, 2-yr feeding/oncogenicity study: Negative for latter at 1,600 ppm.

Rabbit, teratology study: Negative at 25 mg/kg BW, highest level tested. for teratogenic effect on fetuses.

Rat teratology study: Negative at 1,800 ppm, highest dose tested, for teratogenesis.

Rat dominant-lethal study, single ip injection: Negative for mutagenicity at 75 mg/kg BW.

Ames-type mutagenicity test on microorganisms: Negative at up to 1 mg/ml medium, with or without metabolic activation.

Rat, dog, and rabbit metabolism study: Provides evidence for rapid excretion and consistent, high recoveries of administered (labelled dose.

Dermal sensitization test, guinea pig: Negative for contact sensitization.

Cattle, 162-day feeding: Negative at 30 ppm; some weight depression at 100 ppm and slights effects on urinalysis.

Chicken, 1-month feeding: Negative at 1,000 ppm; growth depressed, 2,500 ppm.

Rat, 3-generation reproduction study: NOEL not established, 400 ppm (20 mg/kg BW/day), lower level fed, resulting in significantly lower body weights of weanlings.

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"Free standing summary," continued.

2. Data considered necessary but currently lacking.

   A. A satisfactory repeat rat reproduction is required which includes lower test levels than the study already submitted to establish an unequivocal "no-effect level."

   B. Mutagenicity data are incomplete, but satisfying this requirement can be deferred until EPA has determined the amounts and kinds of mutagenicity data to be required to support a permanent tolerance.

3. Action being taken to obtain the lacking information.

   Petitioner is asked to supply the data.

4. No permanent tolerances have been granted for tebuthiuron.

5. An allowable daily intake for man (ADI) is not available for tebuthiuron. Please see 1. and 2., above.

6. An ADI and a MPI (maximum permissible intake for man) cannot be calculated. Please see 1. and 2., above.

7. We know of no pending regulatory actions regarding registration of the pesticide.

8. Because the adverse effect on reproduction is a minor one; and because the margin of safety - reproduction study's "minimal effect level" (20 mg/kg BW/day) divided by the "theoretical maximum residue contribution" (TMRC) to an average (1.5-kg) daily diet for a (60-kg) adult, 0.0037 mg/kg BW/day - exceeds 5,000 to 1; and because use restrictions further limit human or domestic animal exposure, the requested tolerances (paragraph 1, page 1 of this memo) are judged "safe" to man and to domestic animals.

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Discussion of toxicity of tebuthiuron, cf. PP's 5G1562 and 7F1925.

Tebuthiuron is one of a class of substituted urea herbicides. Other members include monuron, linuron, and diuron.

Other members of the class show effects at fairly low levels, which, as Petitioner points out, include anemia and/or methemoglobinemia. In contrast, tebuthiuron did not cause abnormal hematologic findings in rats or dogs or abnormal bone marrow findings in dogs given up to 50 mg/kg BW/day for 90 days.

In the 90-day study, dogs at 50 mg/kg BW/day did show: Some weight loss; increased relative liver weights and increased in vitro liver O-demethylase activity (on p-nitroaniline) and increased serum alkaline phosphatase - indicative of liver microsomal enzyme induction; and higher blood urea nitrogen values. Two of 4 dogs at 25 mg/kg BW/day had increased relative thyroid weights, and one, increased relative spleen weight. Thus, "no-effect" was set at 12.5 mg/kg BW/day by Mr. D. Ritter (2/21/75 memo, PP 5G1562).

Distinctive pathology in rats, following 90-day feeding at 2,500 ppm, consisted of vacuolization of acinar cells of the pancreas - shown, in separate study, to be partially reversible on removal of tebuthiuron from the diet. These rats, also, showed severe growth retardation. Rats on 400 and 1,000 ppm showed very slight and slight decreases in body weight gain, respectively. Male rats had dose-related increases in relative liver weights and in in vitro liver O-demethylation of p-nitroanisole, presumably due to induction of microsomal enzymes. "No-effect" was set by Mr. Ritter at 1,000 ppm (same memo as in above paragraph).

In preliminary study, female rats, fed tebuthiuron by gavage at 200 mg/kg BW/day on days 6 to 15 of pregnancy, showed weight loss and decreased food consumption; depressed fetal weight; resorptions; and 2/7 deaths. One/7 rats at 100 mg/kg BW/day resorbed 10 fetuses; while 50 mg/kg BW/day did not appear to have adverse effect.

In subsequent rat teratology study, up to 1,800 ppm tebuthiuron in the diet, given on gestation days 6 through 15, was not teratogenic. Maternal weight gain during supplementation was cut 25 and 50% respectively, at 1,200 and 1,800 ppm in the diet, compared to controls. No pancreatic lesions occurred in test rats. Negative for rabbits was 25 mg/kg BW/day.

Two-year studies in rats and mice showed no oncogenic potential for tebuthiuron at up to 1,600 ppm, highest test level.

Rat dominant-lethal and Ames type tests on micro-organisms, with and without metabolic activation, were each negative for mutagenesis.

As noted in our (M. Quaife) memo of 5/22/79, PP 7F1925, rat subchronic, chronic, and 3-generation reproduction studies each showed dose-related growth inhibition, although not significant for lower test-levels in the former two studies. In part for this reason, we find the reproduction study in need of repetition to demonstrate an unequivocal "no-effect level." As with other substituted urea herbicides, growth depression appears to occur in all species in which tebuthiuron is tested at high enough dietary levels.

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RCB finds an analytical method(s) adequate which determines free and bound residues in grass and parent and metabolites in meat (10/13/77. this P

We note that RCB finds analyses of technical tebuthiuron negative for presence of hydrazine and thiourea derivatives, and both technical grade and formulations contain less than 2 ppm and 0.5 ppm, respectively, of N-nitroso derivatives. Tebuthiuron and significant metabolites in both plants and animals contain the thiadiazole moiety. (For sources, cf. RCB memos in PP 5G1562 or 7F1925.)

New submission, Acc. No. 098190, "Review of potential exposure associated with use of Graslan 20F for brush control on rangelands in Texas and Oklahoma," Elanco Products Co., August, 1979, TB comment on.

Claims made in this volume, relating to estimation of "safety" of proposed tolerances, concern (1) amounts of tebuthiuron in diet of cattle who graze on treated rangeland and (2) amounts in the human diet due to tebuthiuron in meat of animals which graze on treated forage.

(1) On p. 6, the report asserts that maximum grass residues would be 5 ppm or less. RCB, however, finds no new residue data in the submission and, therefore, reiterates its previous (4/6/79, PP 7F1925) recommendation for the tolerances (told to the undersigned by Mr. A. Smith, 9/17/79). Moreover, Mr. Smith states that RCB assumes that up to 20 ppm could be consumed by grazing cattle, in determining proper tolerance for grass.

TB finds, based on both laboratory animal and cattle feeding data (cf. freestanding summary of TOX data, pp. 2 and 3, this memo) that a dietary level of 20 ppm tebuthiuron would be without hazard to cattle. Use restrictions detailed by the report, which would be expected to decrease the actual level would, of course, increase the margin of safety.

(2) On pp. 18 et seq. of the report, a "hypothetical worst case situation" for human dietary exposure to tebuthiuron is calculated. However, temporary tolerances, not permanent tolerances, are used by Petitioner to derive a "Theoretical Maximum Residue Contribution" to the average human diet if these tolerances are granted. This is not in accord with TB procedures.

Petitioner, there, also, predicts a decline in dietary exposure to humans, due to a decline in grass residues in first, second, and third years after first use of tebuthiuron on rangeland grass, will occur with resultant decrease in levels in meat. While TB does not deny that such reduction of dietary exposure could occur, TB determines the TMRC assuming that all commodities will bear residues at the tolerance level.

Accordingly, we determine TRMC by present TB procedures, below:

A TMRC of 0.22 mg/day is calculated (cf. computer printout) for the average daily diet (1.5 kg diet/day) for the average (60-kg) adult. This equals ca. 0.0037 mg/kg BW/day.

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Lack of "no-effect" in rat reproduction study precludes calculation of an ADI (TB memo, 5/22/79, this PP).

However, the lower level tested (400 ppm; 20 mg/kg BW/day) may be taken as a "minimal effect level," involving minor adverse effect on reproduction.

Margin of safety, based on this "minimal effect level" is 20 mg/kg BW/day divided by 0.0037 mg/kg BW/day, or in excess of 5,000 to 1.

CONCLUSION: TB finds these requested tolerances safe to man and to domestic animals.

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Appendix, review of TOX data on tech. grade tebuthiuron, previously submitted but not reviewed.

New TOX data, mutagenicity studies:

1. Effect of Lilly compound 75503 (tebuthiuron) on bacterial systems known to detect mutagenic events, J. C. Cline, C. Z. Thompson, R. L. McMahon, Lilly Research Labs., Indianapolis, Indiana, 2/1/78, Acc. No. 247201.

The test compound is identified as "Lilly Compound 75503, tebuthiuron, lot number 9RZ57, 94% pure, technical material."

Procedure. Ames-type test was made with bacterial strains, mutated with respect to histidine requirement, (G46, TA 1535, TA 100, C 3076, TA 1537, D 3052, TA 1538, and TA 98), of Salmonella typhimurium LT-2. In addition, mutant strains of E. coli, with respect to tryptophan (WP2 and WP2 uvrA$^-$) were used. Agar plates, containing minimal amounts of histidine and tryptophan, were prepared which contained a concentration gradient of the test compound of either 0.1 to 1, 0.01 to 0.1,, 0.001 to 0.01, or 0.0001 to 0.001 mg/ml of medium. Similar sets of plates contained microsomal enzyme fraction of liver of rats treated with polychlorinated biphenyl (Arochlor) to induce the enzymes (so-called "S-9" fraction of liver). As positive controls, plates of each type (with and without S-9 present) were prepared with streptozotocin, which is mutagenic without S-9, or with 2-acetylaminofluorene, which is mutagenic only in presence of S-9. After bacterial inoculation, plates were incubated for 48 hrs at 37° C. Non-lethal events are expressed as discrete colonies against a pale background lawn in this procedure, with frequency of colony appearance increasing along the increasing gradient to a concentration at which maximal mutation occurs. Cytotoxicity is shown by a clear zone along the application streak, i.e., lack of background lawn. Minimum inhibitory concentration (MIC) at which cytotoxicity is observed was recorded in the tests.

Results. No plate with test compound showed any evidence of mutagenicity. The minimum inhibitory concentration was greater than 1 mg/ml medium. Positive control 2-acetylaminofluorene was negative with all plates without S-9 present and positive, 0.0001 to 0.1 mg/ml medium, with S-9 for strains TA100, D3052, TA 1538, and TA98. Streptozotocin was positive in gradients comprising extreme limits of 0.00001 to 0.1 mg/ml of medium for strains G46, TA1535, TA100, TA1537, and both WP strains, either with or without S-9 present; it was positive, also, in strain TA98 in absence of S-9.

Conclusion. Under the conditions of this test, technical tebuthiuron is not mutagenic, whether in the presence or absence of metabolic activation.

Appendix, review of TOX data on tech. grade. 2nd p. 000344

New TOX data, mutagenicity studies (contd.).

2. A dominant lethal study with EL-103 (tebuthiuron) in the rat. Study R-655, by D. B. Todd, J. N. Markham, M. V. Owen, W. E. Wilson, and D. M. Morton, Elanco Research Labs., Dec., 1975, Acc. No. 09[illegible].

Test compound is identified as "EL-103, lot number B30-23-119."

Method. Groups of 10 M Harlan (Wistar-derived) rats eached received a single ip injection of either 75 mg/kg EW test material as a 7.5% w suspension in 5% (w/v) gum acacia or equal volume of acacia. Within 4 hours, one proven F was placed with each male and left for 7 days. Then, females were removed and caged individually until gestation day 20 or for 2 weeks. The process of mating each male with one new female for a week was repeated for total period of 8 weeks. Females were killed and number of corpora lutea in the ovary counted. The numbers of viable fetuses and of early and late resorptions in the uterus were determined. For each group of 10 females, mean values were determined. Gestation survival is proportion of fetuses alive. Resorption is proportion of implanted conceptuses that resulted in resorptions. Implantion is proportion of implantations to corpora lutea. Latter three definitions are for correspondingly named indices.

Results. Test compound showed no clinical effects in M's. A female control at week 4 and one at week 6 showed vaginal bleeding and delivered early, respectively. A female mated with test rat, week 1, was edematous; one, at week 2, died on test day 15; and one, at week [illegible], had purulent material in uterus. Eighteen females in control group and 17 in treatment group were not pregnant. All mating trials with one control and one treated male were unsuccessful. Test group resorptions were slightly higher than controls for weeks [illegible] and 7. Ranges of mean live litter size were 9.9 to 13.7 and 8.8 to 12.9 for control and test groups, respectively. All gestation survival indices (control and test, weeks 1 to 8, inclusive) were 1.0. Resorption indices varied from 0.02 to 0.11, with no trend or difference between control and test rats. All implantation indices lay between 0.82 to 0.91, without trends or significant differences.

Conclusion: Under conditions of this test, tebuthiuron tech. is not positive for dominant-lethal effects in the rat.

TOX Cat. Not applicable to mutagenicity studies.

Classif. Supplementary (1. Only one female/male/week of mating was used.

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No_CFR_number Tebuthiuron 9/12/79

File last updated 9/12/79

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ACCEPTABLE DAILY INTAKE DATA

	Dog NOEL mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day/60kg
	$$$$$$$$$	$$$$$$$$	$$$$	$$$$$$$$$$	$$$$$$$$$$

Current Action 7r1925

CROP	Tolerance	Food Factor	mg/day/1.5kg
Cattle(26)	2.000	7.18	0.21553
Goats(62)	2.000	0.03	0.00090
Horses(2us)	2.000	0.03	0.00090
Sheep(145)	2.000	0.19	0.00583

MPI		THRC	% ADI
$$$$$$$$$$	mg/day/60kg	0.2232 mg/day/1.5kg	0.00

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